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IVOR R ELRIFI
MINTZ LEVIN COHN FERRIS
GLOVSKY & POPEO
ONE FINANCIAL CENTER
BOSTON, MA 02111

EXAMINER	
KAM, CHIH MIN	
ART UNIT	**PAPER NUMBER**
1653	13

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/485,571	CALAS ET AL.	
	Examiner	Art Unit	
	Chih-Min Kam	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 January 2002* .

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Oath/Declaration

1. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying the application by application number and filing date is required. See MPEP §§ 602.01 and 602.02. The oath or declaration is defective because non-initialed and non-dated alterations have been made to the address of Inventor, Gerard Grassy. See 37 CFR 1.52(c).

Election/Restrictions

2. Applicant's election with traverse of SEQ ID NO:23 in Paper No. 12 is acknowledged. The traversal is on the ground(s) that only one Group is identified, the peptides in claim 7 are not individually distinct and independent, but are derivatives of the same superfamily of the protein, "protegrins", the peptides in claim 8 are derivatives of the family of the protein "tachyplesins", and the peptides of both claims 7 and 8 are linear peptides that are devoid of a disulfide bond and they are directed to vectoring the active substance in an organism, thus are linked to form a singly general concept. This is not found persuasive because the peptides in the claims do not have in common the same or corresponding structural and technical features. In particular, each peptide is directed to distinct chemical entities; and methods, which use different materials and produce differing effects. For example, the specification (pages 22-23) has shown the internalization ability of various peptides on different cell lines and has demonstrated each peptide has differing effect toward various cells (Tables III and IV), e.g., some peptides such as SM1739 and SM2190 are not internalized while SM2307 and SM2187 penetrate the cell with good efficacy. Accordingly, the claims are not so linked by a special technical feature within the meaning of PCT Rule 13.2 so as to form a single inventive concept

and lack of unity is deemed proper. Therefore, an amino acid sequence of SEQ ID NO:23 and claims 1-17 are examined.

Informalities

The disclosure is objected to because of the following informalities:

3. The specification is objected to for not conforming C.F.R.37 1.822 (d)(1) since the amino acids in the peptide sequences of the invention are listed with one letter abbreviation instead of the required three- letter abbreviation with the first letter as an upper case character. Appropriate correction is required.

Claim Objections

4. Claims 3, 5, 7 and 8 are objected to for not conforming C.F.R.37 1.822 (d) (1) since the amino acids in the peptide sequences have been listed using one letter abbreviation. Use of three-letter format with the first letter as an upper case character is suggested.

5. Claims 3, 5, 7 and 8 are objected to because the claims contain "X", "B" "U" or "O" in the sequence, which should be "Xaa" (See sequence listing). Claims contain amino acid sequences, however, sequence identifier "SEQ ID NO:" is not cited. Please identify each sequence with a "SEQ ID NO:" (See sequence listing).

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

6. Claims 9 and 10 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for

example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for peptides of protegrin analogs and of tachyplesin analogs shown in Tables I and II, which do not have disulfide bond, conjugates of the peptide with doxorubicin or biotin, and the analogs of protegrin and tachyplesin as indicated in the prior art, does not reasonably provide enablement for all peptides derived from all antibiotic peptides, which do not have disulfide bond, a compound containing the peptide, an active substance and a signal agent, and a method of using the peptide to vector an active substance. The specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1-17 encompass a peptide derived from an antibiotic peptide, which does not have any disulfide bond (claims 1-8), a method of using the peptide to vector an active substance (claims 9-10), a compound containing the peptide, an active substance and a signal agent, and the pharmaceutical composition and the diagnostic agent containing the compound (claims 11-17). The specification, however, only discloses cursory conclusions (page 8, line 19-page 13, line 7) without data supporting the findings, which state that the peptide derived from an antibiotic peptide having the formula (I) or (II), or moieties of the peptides, and a compound of formula

(IV) containing the peptide, an active substance and a signal agent, can be used to vector one or more active substances for therapeutic and for diagnostic applications. There are no indicia that the present application enables the full scope in view of various peptides derived from antibiotic peptides as discussed in the stated rejection. The present application provides no indicia and no teaching/guidance as to how the full scope of the claims is enabled. The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the breath of the claims, the presence of working examples, the state of the prior art and relative skill of those in the art, the unpredictability of the art, the nature of the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

(1). The breath of the claims:

The breath of the claims is broad and encompasses unspecified variants regarding the peptides derived from an antibiotic peptide and compounds containing the peptide, an active substance and a signal agent, which are not adequately described or demonstrated in the specification.

(2). The presence of working examples:

The specification only demonstrates certain analogs of protegrin and tachyplesin (Tables I and II), which do not have disulfide bond, and the conjugates of the peptide with doxorubicin or biotin. There are no other working examples indicating the claimed variants or methods in association with the claimed invention.

(3). The state of the prior art and relative skill of those in the art:

The prior art has shown certain analogs of protegrin and tachyplesin (e.g., pages 20-22 in Lehrer *et al.* WO 96/37508), which do not have cysteines, have decreased antimicrobial activity as compared to peptides having disulfide bonds (see sections below under 35 U.S.C. 102 rejection), and the general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide specific guidance to be considered enabling for all variants.

(4). The amount of direction or guidance presented and the quantity of experimentation necessary:

The claimed invention is directed to peptides derived from antibiotic peptides, which do not have any disulfide bond, a method of using the peptide to vector an active substance, a compound containing the peptide, an active substance and a signal agent, and the pharmaceutical composition and the diagnostic agent containing the compound. The specification only indicates certain analogs of protegrin and tachyplesin (Tables I and II) and the conjugates of the peptide with doxorubicin or biotin, and has shown the internalization abilities of various peptides on different cell lines, which was the basis for vectoring an active substance in an organism. However, the specification fails to identify peptides derived from other antibiotic peptides and their internalization abilities on different cell lines. Moreover, the specification has not shown these peptides can internalize into the cell to vector an active substance in an organism. There are no working examples of these methods in the specification. Furthermore, the specification does not provide any specific guidance on the identities of peptides derived from other antibiotic peptides and the internalization abilities of these peptides. Since the specification fails to provide sufficient guidance on the identities of peptides derived from antibiotic peptides and

their internalization abilities, it is necessary to have additional guidance and to carry out further experimentation to assess the internalization abilities of these peptides in order to vector active substances.

(5). Predictability or unpredictability of the art:

As indicated in the previous sections, there are only limited peptides identified as the analogs of antibiotic peptides. Because the amino acid sequences of formulas (I) or (II) and peptides derived from other antibiotic peptides are highly variable, it is not known whether these peptides would have an internalization ability as some peptides shown in Table III and IV. The claims encompass many variants and the invention is highly unpredictable, e.g., the specification has demonstrated different peptide has differing internalization ability toward various cells, some peptides such as SM1739 and SM2190 are not internalized while SM2307 and SM2187 penetrate the cell with good efficacy (Tables III and IV). But for the peptide listed in the table it is not readily apparent that one would have been able to à`priori predict the degree of internalization ability of each peptide.

(6). Nature of the Invention

The scope of the claims includes many structural variants, but the specification has not shown these variants have internalization ability toward various cells nor the same internalization capability for each peptide. Thus, the disclosure is not enabling for reasons discussed above.

In summary, the scope of the claim is broad, while the working example does not demonstrate the claimed variants, the guidance and the teaching in the specification is limited, the art is unpredictable, therefore, it is necessary to have additional guidance and to carry out further experimentation to assess the properties and the use of the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 9 and 10 provide for the use of a peptide obtained from an antibiotic peptide to vector active substances in an organism, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced. Claims 9 and 10 are also indefinite as to "active substance", it is not clear how the peptide vector the active substance, what is the active substance, and what function the active substance has.

9. Claims 1-8, 10 and 11 are indefinite because of the use of the term "derived from an antibiotic peptide or analog thereof". The term "derived from an antibiotic peptide or analog thereof" renders the claim indefinite, it is unclear which peptide is intended as an antibiotic peptide, what amino acid sequence the analogs have, and what amino acid sequence the peptide has as compared to the parent "antibiotic peptide or an analog thereof".

10. Claims 3-8, 10 and 17 are indefinite because of the use of the term "to any one of claims 1", "to one of claim 3", "to any one of claim 1" or "to any claim 1". The term "to any one of claims 1", "to one of claim 3", "to any one of claim 1" or "to any claim 1" renders the claim indefinite, it is unclear regarding the dependency of the claim.

11. A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Note the

explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 3 recites the broad recitation "a succession of at least 5", and the claim also recites "preferably at least 7" which is the narrower statement of the range/limitation; claim 11 recites the broad recitation "n is 0 or more" and "m is 1 or more", and the claim also recites "advantageously 0 or 1" and "preferably up to 10, advantageously up to 5" which is the narrower statement of the range/limitation. Claim 3 is also indefinite because of the use of the term "at least", it is not clear how many consecutive residues of formula (I) or (II) in the peptide? Claim 11 is also indefinte as to "n is 0 or more" and "m is 1 or more", it is not clear what is the number of n or m?

12. Claims 5 and 6 are indefinite because of the use of the terms "Aib" and "Abu". The terms "Aib" and "Abu" render the claim indefinite, it is unclear what the term means. A full name should be indicated at the first occurrence. Claims 5 and 6 are also indefinite as to "[2-thienyl] alanine", it is not clear whether the alanine has the 2-thienyl group since the bracket indicates deletion, and the claim has alanine twice because of the deletion of 2-thienyl. Claim 6 is also indefinite because of the term "such as", the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed

invention. See MPEP § 2173.05(d). It is also not clear in the claim whether or not the amino acid is natrural as to "an amino acid, which may or may not be natural".

13. Claims 7 and 8 are indefinte because the claim contains non-elected sequences.

14. Claims 11-17 are indefinite because of the use of the term "Z represents an active substance" or "Y represents a signal agent". The term "Z represents an active substance" or "Y represents a signal agent" renders the claim indefinite, it is unclear what is the active substance, what function the active substance has, which peptide is intended as a signal agent, and which site the signal agent targets for.

15. Claim 13 is indefinite because of the use of the term "one or more covalent, hydrophobic or ionic bonds". The term "one or more covalent, hydrophobic or ionic bonds" renders the claim indefinite, it is unclear how many covalent, hydrophobic or ionic bonds are formed between peptide (A) and group (Z) or groups (Z) and (Y).

16. Claims 15 is indefinite because of the use of the terms "at least one signal agent (Y)" and "if present". The terms "at least one signal agent (Y)" and "if present" render the claim indefinite, it is unclear how many signal agents are in the compound, and whether or not the signal agent is present in the compound. See also claims 14, 16 and 17 regarding the term "at least".

17. Claim 16 recites the limitation "One compound of formula (TV)" in line 2. There is insufficient antecedent basis for this limitation in the claim. See also claim 17.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

18. Claims 1-6 and 16 are rejected under 35 U.S.C. 102(b) as anticipated by Lehrer *et al.* (WO 96/37508).

Lehrer *et al.* teach various cationic antimicrobial and virus-neutralizing peptides obtained as protegrin analogs have no or one cyteine residue, where any of the 1-4 native cysteines are replaced with a hydrophobic or a small amino acid and various substituents (page 19, lines 35-38), which meets the criteria of claims 1-2. Peptide such as RGGRLAYARRRFAVAWGR is a sequence of formula (I), which meets the criteria of claims 3-5. Peptides which are referred as "snake" forms of the compounds have all cysteines are replaced by X, where X is a small amino acid, especially S and A (page 20, line 34-page 22, line 41), e.g., RGGRLXYXRRRFXVXVGR (Snake form-1), a sequence of formula (V), which meets the criteria of claim 6. Pharmaceutical composition of the peptides is used to inactivate a wide range of microorganisms including bacteria, yeast, protozoa and certain strain of virus (page 28, line 27-page 30, line 15), which meets the the criteria of claim 16.

19. Claims 1-2 and 16 are rejected under 35 U.S.C. 102(b) as anticipated by Masuda *et al.* (Biochem. Biophys. Res. Comm. 189, 845-850 (1992)).

Masuda *et al.* teach a tachyplesin I analog, T10 (KWAFRVAYRGIAYRRAR-NH_2), in which all four cysteines are substituted with Ala, has no appreciable antiviral activity against HIV (page 847; Fig. 1; Table 1), which meets the criteria of claims 1-2 and 16.

20. Claims 1-2 and 16 are rejected under 35 U.S.C. 102(b) as anticipated by Tamamura *et al.* (Chem. Pharm. Bill. 41, 978-980 (1993)).

Tamamura *et al.* teach a tachyplesin I analogs, 4-Ala-T-I, in which all four cysteines are substituted with Ala, and 4Cys(Acm)-T-I, where all cysteines are blocked, have decreased antibacterial activity (page 978; Fig. 1; Table 1), which meets the criteria of claims 1-2 and 16.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102(a) that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

21. Claims 1-5 and 16 are rejected under 35 U.S.C. 102(a) as anticipated by Chang *et al.* (WO 97/18826 (May 1997)).

Chang *et al.* teach an antimicrobial peptide, protegrin PC-8 (RGGRLAYARRRFAVAVGR), which is related to naturally-occurring protegrin peptides and does not have any cysteines, has reduced inhibitory effects against *Neisseria gonorrhoeae* (page 75, lines 29-30; Table 17; Example 12), which meets the criteria of claims 1-5 and 16.

22. Claims 1-5 and 16 are rejected under 35 U.S.C. 102(a) as anticipated by Qu *et al.* (Infection and Immunity 65, 636-639 (February 1997)).

Qu *et al.* teach an antimicrobial peptide, protegrin PC-8 (RGGRLAYARRRFAVAVGR), which is related to naturally-occurring protegrin peptides and does not have any cysteines, has

reduced inhibitory effects against *Neisseria gonorrhoeae* (pages 637-638; Table 1), which meets the criteria of claims 1-5 and 16.

Conclusions

23. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (703) 308-9437. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-0294 for regular communications and (703) 308-4227 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Chih-Min Kam, Ph. D. CMK
Patent Examiner

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February 20, 2002

CHRISTOPHER S. F. LOW
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600